REMARKS

I. Preliminary Remarks

This response is filed in response to the following rejections:

Claims 14 and 17-24 were rejected under 35 U.S.C. §112, first paragraph, as assertedly failing to comply with the enablement requirement.

Claims 14 and 17-24 were rejected under 35 U.S.C. §112, first paragraph, as assertedly failing to comply with the written description requirement.

Claims 20 and 21 were rejected under 35 U.S.C. §112, first paragraph, as assertedly being drawn to new matter under the written description requirement.

Claims 14 and 17-24 were variously rejected under 35 U.S.C. §103, as assertedly unpatentable in view of Russell et al. (*Clinical Genetics*, 1999, 55:389-94, hereinafter "Russell") in view of Czekay et al. (*Mol Biol. Cell* 1999, 8:517-32, hereinafter "Czekay"), further in view of Blattler et al. (*Biochem*, 1985, 24:1517-24, hereinafter "Blattler"), in view of Davis et al (U.S. Patent 6,072,041, hereinafter "Davis"), further in view of Reddy (*Annals of Pharmacology* 2000, 34:915-23, hereinafter "Reddy"), further in view of White et al (U.S. Patent 5,962,266, hereinafter "White"), and further in view of Strom et al (U.S. Patent 6,165,476, hereinafter "Strom").

II. The Subject Matter of the Claims

In general, the subject matter of the claims relates to compositions comprising a receptor activated protein (RAP) conjugated to a lysosomal enzyme.

III. Support for the Amendments

Support for amendment to claim 14 may be found at page 28, lines 4-10, which describes that RAP polypeptides contemplated by the invention include homologs of RAP having 80% sequence identity to native wild type RAP, and at page 30, lines 1-4, which discloses that a RAP contemplated by the invention binds to a LRP.

Support for amendment to claim 20 may be found at page 49, lines 7-22, which discloses that a linker may be from 5-30 atoms long, and further describes wherein the linker may comprise amino acids.

IV. Patentability Arguments

A. The Rejection of Claims 14 and 17-24 under 35 U.S.C. §112, First paragraph, Enablement, May Properly be Withdrawn.

The Examiner rejected claims 14 and 17-24 under 35 U.S.C. §112, first paragraph, as assertedly lacking enablement in the specification. The Examiner contends that Applicants have enabled a RAP conjugate comprising only the human RAP protein and no other species of RAP, and have not enabled a PEGylated derivative or fusion protein comprising the RAP. As such, the claims are allegedly not supported by the specification. Applicants respectfully disagree.

Claim 14 as amended is directed to a composition comprising a RAP polypeptide having at least 80% homology to the RAP set out in SEQ ID NO: 1, wherein the RAP retains binding to a LRP receptor. The specification fully supports the claims as amended. For example, the specification describes methods for making nucleic acid or amino acid substitutions in a polynucleotide or polypeptide sequence (page 61, line 11, to page 63, line 8), and these methods are also well-known to those of ordinary skill in the art. Further, the specification discloses that residues of RAP involved in receptor binding are identified in the art, sets out particular fragments of RAP contemplated by the invention, and describes which sequences are preferred native sequences of RAP (page 28, lines 11-32), thereby providing a worker of ordinary skill an example of residues that may/may not be freely altered in the RAP sequence. Also, the specification discloses the sequences for RAP from other species and provides an alignment of these sequences with the human RAP. This alignment can act as a guide as to which residues are conserved in many RAP proteins (page 27, lines 19-26, and Figure 14), and provide one of ordinary skill a method for determining which residues may be deleted or substituted in RAP homologs. Further, the application teaches one of skill in the art how to generate a RAP homolog with a particular sequence identity using algorithms such as BLAST or PILEUP (pages 21-23), to determine the homology of two similar polynucleotides or polypeptides.

The specification also provides methods for determining if a RAP conjugate binds to LRP (page 54, line 31, to page 55, line 32, and in Example I, page 64), disclosing which types of assays are useful to screen for RAP-LRP binding and to determine functionality of RAP/LRP conjugates. Thus, a worker of ordinary skill reading the

application would be able to make and use a RAP conjugate homologous to SEQ ID NO: 1, which retains the binding to its cognate receptors, based on the disclosure in the specification.

With respect the Examiner's assertion that the application does not enable PEGylation or fusion proteins comprising the RAP conjugate, page 33, lines 5-10, of the specification describes methods for linking chemical derivatives, including polyethylene glycol (PEG), to a RAP conjugate, using techniques well-known to those of ordinary skill. Further, page 50, line 1, to page 51, line 14, teaches methods for making a fusion protein comprising a RAP polypeptide.

As described above, the specification supports the subject matter of claims 14 and 17-24 as amended, and as such, the rejection of the claims under 35 U.S.C. §112, first paragraph, for asserted lack of enablement, should be withdrawn.

B. The Rejection of Claims 14 and 17-24 under 35 U.S.C. §112, First paragraph, Written Description, May Properly be Withdrawn.

The Examiner rejected claims 14 and 17-24 under 35 U.S.C. §112, first paragraph as assertedly lacking written description in the specification. The Examiner alleges that Applicants have described a RAP conjugate comprising only the human RAP protein and have allegedly not described all RAP species assertedly encompassed by the claims. Applicants respectfully disagree.

Claim 14 as amended is directed to a composition comprising a RAP polypeptide having at least 80% homology to the RAP set out in SEQ ID NO: 1, wherein the RAP retains binding to a LRP receptor. As stated above, the specification describes a RAP protein with 80% homology to SEQ ID NO: 1 which retains binding to a LRP, thus, a worker of skill in the art reading the specification would recognize that the inventors were in possession of the claimed subject matter at the time of filing.

As such, the rejection of the claims under 35 U.S.C. §112, first paragraph, as allegedly lacking written description, should be withdrawn.

C. The Rejection of Claims 20 and 21 under 35 U.S.C. §112, First Paragraph, Written Description, May Properly be Withdrawn.

The Examiner rejected claims 20 and 21 under 35 U.S.C. §112 as assertedly lacking written description, being based on subject matter that was not contained in the original filing.

Amendment of claim 20 to recite 5 to 30 amino acids obviates the rejection. Support for the amendment is found for example, on page 49, lines 7-22, which discloses that the linker may be from 5-30 atoms long, and further describes wherein the linker may comprise amino acids.

Support for the recitation of PEGylation in claim 21 may be found, for example, at page 33, lines 5-10, which teaches that the RAP polypeptide may be conjugated to polyethylene glycol using methods well-known in the art. As such, the recitation of PEGylation in the claims was described in the application as filed, and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

D. The Rejection of Claims 14, 17, 19, and 22 under 35 U.S.C. §103, May Properly be Withdrawn.

1. The Examiner rejected claims 14, 17, 19 and 22 under 35 U.S.C. §103, as allegedly being obvious and unpatentable over Russell, which assertedly teaches targeting of recombinant proteins to specific cellular compartments in treatment of disease, in view of Czekay, which teaches that a RAP-GST fusion protein enters the lysosome of a cell. Applicants respectfully disagree. A worker of ordinary skill in the art would not be motivated by the disclosure of Czekay to attach a lysosomal enzyme to a RAP protein to arrive at a treatment as assertedly disclosed in Russell. Moreover, the present disclosure is the first disclosure that a RAP fusion protein enhances uptake of a RAP fusion protein into the cell.

As Russell discloses, therapies are already underway to administer lysosomal enzymes to patients having lysosomal storage disorders, such as Pompe's disease. Studies show that recombinant alpha-glucosidase enters into the lysosome, likely through the mannose-6-phosphate receptor, without need for a fusion protein that targets the enzyme to its natural locale (Russell, page 390, col. 2, citing Pfeffer et al. "Targeting of proteins to the lysosome" *Curr Top Microbiol Immunol* 1991, 170:43-63). In fact, Russell indicates that this

discovery generated excitement in the field, and studies subsequent to Russell have demonstrated the efficacy of recombinant enzyme in human patients (see for example, Van den Hout et al., *J Inherit Metab Dis* 2001, 24:266-74; Winkel e al., *Ann Neurol* 2004, 55:495-502; and, Van den Hout et al., *Pediatrics* 2004, 113:e448-57, abstracts submitted herewith).

Czekay teaches that RAP-GST is delivered to the lysosome after internalization of the megalin/RAP complex, but does not indicate that this would be a beneficial method for targeting proteins to the lysosome. Czekay does not indicate that there is a benefit, e.g. enhanced uptake or decreased protein degradation, to using the RAP protein as a targeting protein. Additionally, studies indicate that RAP injected intravenously is cleared rapidly from the plasma (Warshawsky et al., *J Clin Invest.* 2001, 92:937-44, submitted herewith), which is a well-known shortcoming of many pharmaceutical agents (Warshawsky et al., page 941, col. 2).

Thus, there is no reason for one of skill in the art reading the disclosure of Russell, which teaches that recombinant lysosomal enzymes effectively targets to the lysosome, to look to the disclosure of Czekay, which teaches that RAP traffics to the lysosome and is degraded, to attempt to direct a lysosomal protein to the lysosome using a RAP fusion protein. One of ordinary skill would not be motivated to generate a fusion protein for targeting protein to the lysosome, without an expected benefit from the fusion protein, when the protein of interest (e.g., GAA) already enters the lysosome through another targeting mechanism and shows significant efficacy in treating disease. Moreover, the art suggests that RAP may not be the most advantageous protein with which to develop a pharmaceutical conjugation since it is rapidly cleared from serum.

Also, the present disclosure is the first teaching that RAP conjugated to a second protein increases the entry of proteins into the lysosome; uptake of a RAP-GAA conjugate into target cells is up to 60 times greater than uptake of recombinant GAA alone (see specification Example IV, page 69). It is unexpected that fusion of a lysosomal enzyme to a second protein that traffics to the lysosome would dramatically increase the uptake of the lysosomal enzyme.

Because one of ordinary skill in the art reading Russell would not be motivated to combine the teachings with the disclosure of Czekay to arrive at the subject matter of the claims, and because the present application is the first disclosure of the

unexpected result that a RAP-conjugated lysosomal enzyme would enter the lysosome with greater capacity than the enzyme alone, the rejection of claims 14, 17, 19 and 22 under 35 U.S.C. §103 should be withdrawn.

2. The Examiner rejected claim 18 under 35 U.S.C. §103, as assertedly unpatentable over Russell, in view of Czekay, further in view of Blattler, which assertedly discloses protein cross-linking agents for linkage of two proteins. As discussed above, it would not be obvious for a worker of ordinary skill in the art to generate a RAP-lysosomal enzyme conjugate based on the disclosures of Russell and Czekay, and as such, it would not be obvious to link them using cross-linking agents disclosed by Blattler.

3. The Examiner rejected claim 20 under 35 U.S.C. §103, as assertedly unpatentable over Russell, in view of Czekay, further in view of Davis, which assertedly discloses fusion proteins joined by a linker of less than 50 amino acids. As discussed above, it would not be obvious for a worker of ordinary skill in the art to generate a RAP-GAA conjugate based on the disclosures of Russell and Czekay, and as such, it would not be obvious to link them together using a linker of less than 50 amino acids as disclosed by Davis.

4. The Examiner rejected claim 21 under 35 U.S.C. §103, as assertedly unpatentable over Russell, in view of Czekay, further in view of Reddy, which assertedly discloses that PEG may be linked to a protein, which can confer advantages in delivery of a pharmaceutical. As discussed above, it would not be obvious for a worker of ordinary skill in the art to generate a RAP-lysosomal enzyme conjugate based on the disclosures of Russell and Czekay, and as such, it would not be obvious to conjugate a PEG moiety to either protein comprising the conjugate as disclosed by Reddy.

5. The Examiner rejected claims 23 and 24 under 35 U.S.C. §103, as assertedly unpatentable over Russell, in view of Czekay, further in view of White or Strom, which assertedly disclose pharmaceutical formulations for administration of an agent intravenously or via inhalation, respectively. As discussed above, it would not be obvious for a worker of ordinary skill in the art to generate a RAP-lysosomal enzyme conjugate based on the disclosures of Russell and Czekay, and as such, it would not be obvious prepare the conjugate as a pharmaceutical composition for administration intravenously as in White, or via inhalation as in Strom.

E. Double Patenting

The Examiner provisionally rejected claims 14, 17-20 and 22 under the doctrine of obviousness-type double patenting as unpatentable over claims 1-16 of co-pending, co-owned application No. 10/812,849, in view of Russell. Applicants submit that application no. 10/812,849 is a continuation-in-part of the present application, having a later filing date and publication date than the present application. One of skill in the art could not have motivation combine this reference with Russell at the time of filing to derive the claimed subject matter.

Applicants note the Examiner's rejection and will address the issue when claims have issued in one of the applications.

V. Conclusion

Applicants submit that all claims are in condition for allowance and request an early notification of the same. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

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Respectfully submitted,

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